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PTO/SB/05 (4/98)
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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No.	UF-242X
First Inventor or Application Identifier	Josef Neu
Title	Dipeptides For Prevention Of Muscle Breakdown And Microbial Infection
Express Mail Label No.	EK507535848

jc882 U.S. PTO 09/636491 08/11/00

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility patent application contents

ADDRESS TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231

1. [X] * Fee Transmittal Form (e.g., PTO/SB/17) (Submit an original and a duplicate for fee processing)
2. [X] Specification [Total Pages 10] (preferred arrangement set forth below)
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings (if filed)
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [ ] Drawing(s) (35 U.S.C. 113) [Total Sheets]
4. Oath or Declaration [Total Pages 2]
   a. [X] Newly executed (original or copy) unsgined
   b. [ ] Copy from a prior application (37 C.F.R. § 1.63(d)) (for continuation/divisional with Box 16 completed)
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

*NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

5. [ ] Microfiche Computer Program (Appendix)
6. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
   a. [ ] Computer Readable Copy
   b. [ ] Paper Copy (identical to computer copy)
   c. [ ] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. [ ] Assignment Papers (cover sheet & document(s))
8. [ ] 37 C.F.R.§3.73(b) Statement (when there is an assignee) [ ] Power of Attorney
9. [ ] English Translation Document (if applicable)
10. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
11. [ ] Preliminary Amendment
12. [X] Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
13. [X] * Small Entity Statement(s) (PTO/SB/09-12) [ ] Statement filed in prior application, Status still proper and desired
14. [ ] Certified Copy of Priority Document(s) (if foreign priority is claimed)
15. [X] Other: Claims priority to USSN 60/149,369, filed August 13, 2000

16. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment:
[ ] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No. ______/______
Prior application information: Examiner ______ Group / Art Unit: ______

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

17. CORRESPONDENCE ADDRESS

[ ] Customer Number or Bar Code Label (Insert Customer No. or Attach bar code label here) 23557 or [ ] Correspondence address below

PATENT TRADEMARK OFFICE

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Name (Print/Type)	David R. Saliwanchik	Registration No. (Attorney/Agent)	31,794
Signature	David Saliwanchik	Date	Aug. 11, 2000

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Applicant or Patentee: Josef Neu Attorney's
Serial or Patent No.: Docket No. UF-242X
Filed or Issued:
For: Dipeptides For Prevention Of Muscle Breakdown And Microbial Infection

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY
STATUS (37 CFR 1.9 (f) and 1.27 (c)) – NONPROFIT ORGANIZATION

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

NAME OF ORGANIZATION University of Florida
ADDRESS OF ORGANIZATION 223 Grinter Hall
Gainesville, FL 32611

TYPE OF ORGANIZATION

[X] UNIVERSITY OR OTHER INSTITUTION OF HIGHER EDUCATION
[ ] TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a)(3))
[ ] NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA
(NAME OF STATE)
(CITATION OF STATUTE)
[ ] WOULD QUALIFY AS TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 USC 501(a) and 501(c)(3) IF LOCATED IN THE UNITED STATES OF AMERICA
[ ] WOULD QUALIFY AS NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA IF LOCATED IN THE UNITED STATES OF AMERICA
(NAME OF STATE)
(CITATION OF STATUTE)

I hereby declare that the above identified nonprofit organization qualifies as a nonprofit organization as defined in 37 CFR 1.9 (d), for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, with regard to the invention described in the above-identified:

[ ] PATENT [X] APPLICATION

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization identified above with regard to the above-identified invention.

If the rights held by the above identified nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9 (d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9 (d) or a nonprofit organization under 37 CFR 1.9 (e).

*NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring their status as small entities. (37 CFR 1.27)

NAME
ADDRESS
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

NAME
ADDRESS
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change of status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28 (b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Thomas E. Walsh, Ph.D.
TITLE IN ORGANIZATION Director of Sponsored Research
ADDRESS OF PERSON SIGNING 223 Grinter Hall
Gainesville, FL 32611
SIGNATURE T Walsh DATE August 11, 2000

DESCRIPTION

DIPEPTIDES FOR PREVENTION OF MUSCLE BREAKDOWN AND MICROBIAL INFECTION

Cross-Reference to Related Application

This application claims the benefit of U.S. Provisional Application No. 60/149,369, filed August 13, 1999.

Background of the Invention

Prevention or inhibition of muscle breakdown, and the facilitation of efficient muscle repair is of great interest to athletes, the elderly, and those with muscle-wasting conditions. A wide range of products and methods have been proposed for enhancing healthy muscle tissues and enhancing athletic performance. Existing compositions and methods which are available for these purposes suffer from a variety of shortcomings. These shortcomings range from potentially dangerous side affects, to a lack of bioavailability and difficulty in formulation and/or administration.

It is well known that proteins are converted to amino acids in the digestive system and that the resulting amino acids are used by the body for growth and development. In certain medical situations a patient may be unable to receive proteins. In these situations patients have been given free amino acids. Free amino acids, however, are sometimes not tolerated well by patients and may cause diarrhea and dehydration. Also, the free amino acids may be unstable and/or difficult to formulate.

It has been observed that the body can more effectively absorb certain small molecules called dipeptides or tripepetides. These molecules consist of, for example, two to three amino acids. It has been observed, for example, that peptides containing the amino acid residue glycine in the N-terminal position are readily assimilable. See for example, U.S. Patent No. 4,340,592.

European Patent Application No. 0,182,356 discloses a nutritional composition containing at least one oligopeptide consisting of a dipeptide or a tripeptide wherein the N-terminal amino acid residue is selected from the class consisting of alanine, lysine and arginine.

One group conducting research in this area concluded that glycine is generally superior to other amino acids as the N-terminal amino acid residue in a dipeptide. This superiority was attributed to a greater fraction of such an intravenously administered dipeptide reaches the tissues. S. Adibi *et al.*, *Influence of Molecular Structure on Half-life and Hydrolysis of Dipeptides in Plasma: Importance of Glycine as N-Terminal Amino Acid Residue*, 35 Metabolism 850, 835 (1986).

Two European patents, 0,087,751 and 0,087,750 disclose water-soluble peptides. The '751 patent discloses a method to parenterally administer low water-soluble amino acids. Two amino acids, tyrosine and cystine, individually have low solubility in water. These amino acids, however, are clinically useful and, therefore, it was desirable to find an effective formulation. The '751 patent describes an infusion method which involves bonding these relatively insoluble amino acids to the amino acid lysine to produce a tripeptide.

The '750 patent discloses the infusion of glutamine as a derivative substituted by α-aminoacyl residues on the α amino group. That is, glutamine is in the "c-terminal" position, in that its alpha amino nitrogen becomes part of the peptide bond with the other amino acid. The preferred dipeptide preparation disclosed in the '750 patent is alanyl-glutamine. The aminoacylation of glutamine is reported to achieve a stabilization of the terminal amide group.

Experiments involving the use of total parenteral nutrition (TPN) containing glycyl-glutamine dipeptides, however, suggest potential adverse effects of the TPN formulation containing glycyl-glutamine (U.S. Patent no. 5,189016).

Two commercially available dipeptides of glutamine are Dipeptiven, which is an alanyl-glutamine (Fresenius Laboratories, Germany) and Glamin (Pharmacia and Upjohn Laboratory, Sweden), which is an amino acid solution containing glycyl-glutaminedipeptide. To this date, there are no studies of the arginyl-L-glutamine dipeptide.

It is well known that nutrition can impact the functioning of the immune system. Proper nutrition can promote healthy immune responses. There are many aspects to the immune response of humans and animals. One component of the immune response is mucosal immunity. Mucosal immunity provides a first line of defense for the body against a broad range of pathogens.

There remains a great need in the art for compositions and methods which promote healthy muscle tissue, reduce muscle deterioration, and/or promote a healthy immune system.

Brief Summary of the Invention

In one embodiment, the subject invention provides materials and methods useful in promoting healthy muscle tissue. The promotion of healthy muscle tissue according to the subject invention is particularly advantageous for athletes and others engaging in rigorous physical exertion and/or training. The promotion of healthy muscle tissue according to the subject invention is also advantageous for the treatment and/or prevention of muscle wasting conditions. This is particularly advantageous for critically ill hospitalized patients including neonates.

The compositions of the subject invention are also useful in promoting mucosal immunity. Such immunity, which is often typified by an IgA response, can be a critical defense against a variety of human and animal pathogens. These pathogens may be, for example, bacteria, viruses, or parasites.

In a preferred embodiment of the subject invention, the amino acids arginine and glutamine are combined as the dipeptide arginyl-glutamine in order to provide beneficial effects in a safe, easily absorbable formulation. The dipeptide of the subject invention promotes healthy muscle tissue and an advantageous immune response. The dipeptide of the subject invention is also advantageous because it is safe for human or animal consumption and can be readily formulated in an aqueous solution for internal consumption.

The compositions of the subject invention can be used in a variety of situations where it is desired to promote healthy muscle tissue. For example, the dipeptides of the subject

invention can be used in medical applications to aid critically ill patients. Also, the arginyl-glutamine dipeptide can be applied to enhance athletic performance.

The compositions can also be used to promote a healthy immune system in humans or animals. This is particularly advantageous for patients and hospital workers, or others who may be exposed to pathogens.

These peptides of the subject invention can be administered as one component of a nutrient composition. The use of these peptides, compared to the administration of equivalent amounts of the free amino acids, cause a decrease in osmolarity of the solution, facilitate the administration of amino acids having low water solubility, and stabilize heat unstable amino acids such as glutamine. The aqueous solution is suitable for intravenous feeding or for intragastrointestional administration. The aqueous solution itself may contain other nutrient additives such as fats, glucose, mono- or oligo-saccharides, minerals, trace elements and/or vitamins.

Detailed Disclosure of the Invention

The present invention relates to nutrient compositions containing dipeptides and methods for administering the same. Advantageously, the subject invention provides a dipeptide having water solubility, stability to sterilization, long-term stability, and bioavailability for humans and animals. A preferred embodiment of the present invention provides a nutrient composition comprising an aqueous solution having at least one arginyl-glutamine dipeptide.

Among the advantages of the dipeptide of the subject invention over the existing alanyl-glutamine and glycyl-glutamine dipeptides is that the arginine moiety is particularly advantageous because it is a creatine phosphate precursor, a stimulator of immune function, a stimulator of growth hormone production and, in combination with glutamine, is particularly useful in strengthening mucosal immune defenses.

In one embodiment of the subject invention the arginyl-glutamine dipeptides described herein are useful for promoting healthy muscle tissue. Thus, these dipeptides can be used by athletes or others who are undergoing training or other rigorous physical exertion.

The dipeptide compositions of the subject invention can also be used to promote muscle repair and maintenance in hospital or hospice patients, or other individuals subject to muscle deterioration.

In a further embodiment, the subject invention provides materials and methods for enhancing the immune system functioning of humans and animals. In this embodiment, compositions which comprise the arginyl-glutamine dipeptide are administered to people or animals who could benefit from an improved immune response. Specifically, the dipeptides of the subject invention can be used to enhance mucosal immunity. This enhancement of mucosal immunity reduces the risk of infection by a variety of pathogens including bacteria, viruses, and parasites.

In view of the muscle maintenance characteristics of the arginyl-glutamine dipeptide combined with its ability to stimulate an effective immune response, the compositions of the subject invention are particularly attractive for use in hospitals. For example, compositions containing the dipeptide of the subject invention can be used to maintain muscle mass in inactive patients while having the added benefit of reducing susceptibility to hospital acquired infections in patients.

In accordance with the teachings provided herein, aqueous clinical nutrient compositions can be prepared which include at least one arginyl-glutamine dipeptide. The dipeptide can be added to enteral or parenteral formulations of either complete or incomplete nutritional content. Each dipeptide has an N-terminal amino acid which is arginine. The C-terminal amino acid is glutamine.

The concentration of the dipeptide in the aqueous solution can be, for example, from about 0.1 to about 25.0 percent by weight. In addition to dipeptides, the clinical nutritional solution can contain, for example, dextrose, liquid emulsions, vitamins, minerals and trace elements. The selection of the particular dipeptide formulation depends upon the particular use.

Dipeptide additives such as single or multiple entities, as well as a total nutritional formulation which contains dipeptides as one component among many are contemplated by this invention.

The aqueous dipeptide formulation may be ingested orally along with other nutrients such as conventional foods or prepared vitamins, fats, glucose or other mono-saccharides, oligosaccharides, minerals and trace elements. For parenteral administration, a supply of the dipeptide solution may be merged through a Y-connection with a supply of glucose solution or other parenteral solutions. The dipeptide solutions may be mixed with glucose solutions and/or other parenteral solutions to create a mixture which may be administered parenterally.

The administration of dipeptides rather than free amino acids allows administration of the same amount of amino acid residue in solutions which are less hypertonic and therefore can be introduced into peripheral veins.

The dipeptides of the subject invention can be readily synthesized and/or formulated by a person skilled in the art having the benefit of the instant disclosure. Alternatively, the dipeptides can be purchased commercially from, for example, Bachem Biosciences, Inc. which sells the H-Arg-Glu-OH salt.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims.

Claims

I claim:

1. A peptide composition comprising an arginyl-glutamine dipeptide formulated as a nutrient formulation, wherein the arginine residue is the amino terminus of said dipeptide and the glutamine residue is the carboxy terminus of said dipeptide.

2. The peptide composition, according to claim 1, wherein said formulation is suitable for enteral administration.

3. The peptide composition, according to claim 1, wherein said formulation is suitable for parenteral administration.

4. The peptide composition, according to claim 1, wherein the concentration of said dipeptide is from about 0.1% to about 25.0% by weight of said formulation.

5. The peptide composition, according to claim 1, wherein said nutrient formulation comprises an additive selected from the group consisting of vitamins, minerals, trace elements, fats, monosaccharides and oligosaccharides.

6. The peptide composition, according to claim 5, wherein said monosaccharide is glucose.

7. A method for promoting healthy muscle tissue in a human or animal, said method comprising administering to a human or animal in need of such treatment an effective amount of a dipeptide composition comprising an arginyl-glutamine dipeptide formulated as a nutrient formulation, wherein the arginine residue is the amino terminus of said dipeptide and the glutamine residue is the carboxy terminus of said dipeptide.

8. The method, according to claim 7, wherein said human or animal has undergone, is undergoing, or will undergo physical exertion or training.

9. The method, according to claim 7, wherein said human or animal is in need of maintenance of muscle mass.

10. The method, according to claim 9, wherein said human or animal is hospitalized.

11. The method, according to claim 10, wherein said hospitalized human or animal is a neonate.

12. The method, according to claim 9, wherein said human or animal is subjected to an environment of decreased gravity relative to gravity on earth.

13. A method for promoting increased immunity to pathogens in a human or animal, said method comprising administering to a human or animal in need of such treatment an effective amount of a dipeptide composition comprising an arginyl-glutamine dipeptide formulated as a nutrient formulation, wherein the arginine residue is the amino terminus of said dipeptide and the glutamine residue is the carboxy terminus of said dipeptide.

14. The method, according to claim 13, wherein said human or animal is at risk for infection by a pathogen.

15. The method, according to claim 14, wherein said pathogen is selected from the group consisting of bacteria, viruses and parasites.

16. The method, according to claim 13, wherein said human or animal is an employee, worker or patient in a hospital or medical facility.

17. The method, according to claim 13, wherein said immunity is mucosal immunity.

18. The method, according to claim 17, wherein said mucosal immunity comprises an IgA response to said pathogen.

Abstract of the Disclosure

The subject invention provides dipeptides useful in promoting healthy muscle tissues as well as effective immune responses. The dipeptides of the subject invention are particularly advantageous because they are stable, bioavailable, and can be formulated in an aqueous solution.

DECLARATION (37 CFR 1.63) AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name; and

I believe that I am the original, first, and sole inventor (if only one name is listed below), or an original, first, and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **Dipeptides For Prevention Of Muscle Breakdown And Microbial Infection**, specification for which

☐ is attached hereto.

☐ was filed _____, Serial No. _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code §119 and/or §365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Application Serial No.	Country	Filing Date	Priority Claimed

I hereby claim priority benefits under Title 35, United States Code §119 of any provisional application(s) for patent listed below:

Application Serial No.	Filing Date	Priority Claimed
60/149,369	13 August 1999	Yes

I hereby claim the benefit under Title 35, United States Code, §120 and/or §365 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (Patented, Pending, Abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following persons registered to practice before the Patent and Trademark Office as my attorneys with full power of substitution and revocation to prosecute this application and all divisions and continuations thereof and to transact all business in the Patent and Trademark Office connected therewith: David R. Saliwanchik, Reg. No. 31,794; Jeff Lloyd, Reg. No. 35,589; Doran R. Pace, Reg. No. 38,261; Christine Q. McLeod, Reg. No. 36,213; Jay M. Sanders, Reg. No. 39,355; James S. Parker, Reg. No. 40,119; Frank C. Eisenschenk, Reg. No. 45,332; Jean Kyle, Reg. No. 36,987; Seth M. Blum, Reg. No. 45,489; Glenn P. Ladwig, Reg. No. P-46-853.

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352-375-8100

Docket No. UF-242X

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Signature of First or Sole Inventor

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Residence ______________________ Citizenship ______________________

Post Office Address ______________________

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______________________ Date ______________________

Signature of Second Joint Inventor

****

Name of Third Joint Inventor ______________________

Residence ______________________ Citizenship ______________________

Post Office Address ______________________

____

______________________ Date ______________________

Signature of Third Joint Inventor

****

Name of Fourth Joint Inventor ______________________

Residence ______________________ Citizenship ______________________

Post Office Address ______________________

____

______________________ Date ______________________

Signature of Fourth Joint Inventor